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Original article

Twelve-year mortality in HIV-infected patients receiving antiretroviral therapy (ART): the role of social vulnerability. The ANRS CO8 APROCO-COPILOTE cohort

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Abstract

Background: Although the role of clinical/biological factors associated with mortality has already been explored in HIV-infected patients on ART, to date little attention has been given to the potential role of social vulnerability. This study aimed to construct an appropriate measure of social vulnerability and to evaluate whether this measure is predictive of increased mortality risk in ART-treated patients followed up in the ANRS CO8 APROCO-COPILOTE cohort.

Methods: The cohort enrolled 1,281 patients initiating a protease inhibitor-based regimen in 1997-1999. Clinical/laboratory data were collected every 4 months. Self-administered questionnaires collected psycho-social/behavioural characteristics at enrolment (M0), M4, and every 8-12 months thereafter. A Multiple Correspondence Analysis using education, employment and housing indicators helped construct a composite indicator measuring social vulnerability. The outcome studied was all-cause deaths occurring after M4. The relationship between social vulnerability and mortality, after adjustment for other predictors, was studied using a shared-frailty Cox model, taking into account informative study dropout.

Results: Over a median [IQR] follow-up of 7.9 [3.0;11.2] years, 121 deaths occurred among 1,057 eligible patients, corresponding to a mortality rate of [95%CI]=1.64[1.37;1.96]/100 person-years. Leading causes of death were non-AIDS defining cancers (n=26), AIDS (n=23), and cardiovascular diseases (n=12). Social vulnerability (HR[95%CI]=1.2[1.0;1.5]) was associated with increased mortality risk, after adjustment for other known behavioural and bio-medical predictors.

Conclusions: Social vulnerability remains a major mortality predictor in ART-treated patients. A real need exists for innovative interventions targeting individuals cumulating several sources of social vulnerability, to ensure that social inequalities do not continue to lead to higher mortality.

Running head: Mortality in HIV-infected patients on ART: the role of social vulnerability

Introduction

Enough evidence exists today to show that HIV-related mortality has been greatly reduced since the introduction of potent antiretroviral therapy (ART) (1, 2). Indeed, HIV-infected patients who are not drug users or coinfecting with hepatitis C virus (HCV) now tend to have mortality rates similar to those observed in the general population, at least in high-income North American and European countries (3-5). Known factors leading to higher HIV-related mortality include delayed HIV screening (6, 7), delayed care (8-10), non-adherence to treatment (11, 12), exposure to certain antiretroviral agents (13), accelerated aging driven by residual immune activation (14), and finally, co-occurrence of other virus/diseases (*e.g.*, hepatitis C) (3, 15). In addition, certain lifestyle factors such as smoking, alcohol consumption and drug use may also contribute to increase the risk of mortality (16-18).

Social vulnerability can be regarded more as a structural-level exposure, related to the risk environment framework, than as an individual factor (19). It can potentially interfere with patient response to ART, through reduced access to the different components of the optimal HIV care cascade (HIV screening, referral to HIV care, access to HIV treatment) (20-23).

Before the arrival of ART, results regarding the impact of socio-economic status on mortality of HIV-infected patients were heterogeneous, with some studies outlining no impact (24, 25), while others highlighted the opposite (26, 27). The impressive increase in survival rates thanks to ART has facilitated increased research into competing risk factors of mortality, including unhealthy behaviors (16-18) and low socio-economic status (28, 29). However, some heterogeneity still remains in post-ART studies, perhaps due to major differences in the United States' health system (28, 30) and those in Canada (29) or Western European (31-33) countries, or to the fact that different socio-economic indicators, measured at household or regional level, were used as predictors of mortality (28, 29, 34). To date, several European studies focusing on HIV-positive individuals have found an association between mortality and either education level (7, 31, 32) or income (33), but few have tried to measure social vulnerability and instability in a more complete manner (35). Socio-economic status and education are important components of social vulnerability but they have been rarely combined to create a more complex indicator. Although educational level is already known to be a predictor of increased mortality in the general population (36, 37), few studies have explored the complexity of the relationship between educational level and other socio-economic indicators in HIV-infected patients. Furthermore, none has linked such a global indicator of social vulnerability to survival rates.

We used the 12-year French ANRS CO8 APROCO-COPILOTE cohort follow-up of HIV-infected individuals, started on ART in 1997-1999, to develop an original combined indicator of social vulnerability, based on different proxies of socioeconomic status measured at baseline, and to evaluate whether this indicator, is a significant predictor of mortality, independently of other clinical and behavioural predictors. In our study, we decided to exclude early mortality (*i.e.* deaths arising during the first 4 months after ART initiation), which are mainly due to pre-existing severe clinical and immunovirological statuses before ART initiation, as initial ART exposure could not have prevented this early mortality.

Methods

Study design

The APROCO-COPILOTE cohort was designed to study the clinical, immunological, virological, and socio-behavioural course of HIV disease in HIV-1 infected individuals who started the first generation of combined antiretroviral regimens, which included protease inhibitors (PI). Between May 1997 and June 1999, patients (n=1,281) were enrolled in the cohort in 47 centres throughout France, at their first ART prescription, and clinically followed up every 4 months thereafter until the end of the study (month 144, written M144).

Data Collection

At each follow-up visit, the supervising HIV physician completed a form that included the patient's clinical and laboratory data, including HIV CDC clinical stage defined by the Centers for Disease Control and Prevention (CDC) (38), plasma HIV RNA level, CD4⁺ cell count, hemoglobin concentration, aspartate and alanine transaminase (AST, ALT) levels, platelet count, serum creatinine level and weight.

The medical questionnaire at enrolment included additional data about the patient's HIV history: HIV transmission category (intravenous drug use (IDU), sex between men, or other), time since HIV diagnosis, exposure to antiretroviral treatment before enrolment in the cohort, time since ARV initiation, and coinfection with HCV at M0.

At M0, M4, and every 8 months thereafter during the first five years of follow-up, and then every 12 months thereafter, a self-administered questionnaire collected data on socio-demographic characteristics including age, gender, having a steady partner or not and indicators of social status such as education level, employment status, housing stability and housing comfort. These questionnaires also gathered information about patients' behaviours (adherence to ART, tobacco and alcohol consumption) and experience with the disease and its treatment (self-reported side effects, depressive symptoms).

Participants

For the present analysis we selected all patients who completed the self-administered questionnaire at enrolment (M0) and at least one other self-administered questionnaire or who died after the first 4 months of follow-up (n=1,057). The study period targeted the follow-up period between M4 and M144, and only visits where a corresponding self-administered questionnaire was administered were included in the analysis.

Variables

The outcome used in this analysis was deaths (from all causes) occurring between M4 and M144 in the selected patients. The overall mortality rate was computed as the number of deaths occurring between M4 and M144 over the number of person-years during the study period. A composite continuous indicator of social vulnerability was created using a Multiple Correspondence Analysis (MCA), performed on the basis of the following socio-economic binary indicators measured at M0: having a high school certificate (yes/no), being employed (yes/no), having stable housing (yes/no), and having comfortable housing (yes/no). The composite continuous indicator was defined by the first of the two factors (with reversed sign) identified in the MCA solution.

The following eight clinical variables were tested in the multivariate analysis to adjust for potential predictors of mortality and confounding effects: AIDS stage; being antiretroviral naive

at M0; time since HIV diagnosis; plasma HIV RNA >100,000 copies/mL at M0; poor early immune status (CD4 counts/mm³ <200 at both M0 and M4); a validated indicator of advanced liver fibrosis (defined as FIB-4 >3.25 (39), where FIB-4 is an index based on age, AST, ALT and platelet count (39, 40)); anaemia (defined as a haemoglobin concentration <12 g/dL for women and <13 g/dL for men); a validated indicator of renal impairment based on estimated creatinine clearance (ECC), computed using the Cockcroft-Gault formula (with ECC <60 mL/min defining moderate/severe renal impairment) (41).

Furthermore, the following seven self-reported psychosocial and behavioural characteristics were measured and tested in the multivariate analysis: presence of depressive symptoms (using an indicator based on the validated French version of the Center for Epidemiologic Studies Depression Scale (CES-D) scale, and defined as a CES-D score > 17 in men and > 23 in women) (42); tobacco smoking (using a binary indicator based on the average number of cigarettes smoked daily during the 4 previous weeks (smoking > 20 cigarettes/day)); average daily alcohol consumption (43) (with the following categories: no consumption, low (\leq 1 alcohol units (AU)/day), moderate (1–3 AU/day for women and 1–4 AU/day for men), and elevated (>3 AU/day for women and >4 AU/day for men)); regular binge drinking (i.e. drinking \geq 5 AU on one occasion, at least once a month); perceived side-effects (using a score based on a 13-item scale of self-reported symptoms and the discomfort they caused, in accordance with the French version of the symptom index developed by Justice *et al* (44), and described elsewhere (45); adherence to ART (using a three-level score (high, moderate and low adherence) based on a validated algorithm using the ART doses, both prescribed and those actually taken, during the previous 4 days (46), according to the methodology established by the AIDS Clinical Trial Group (47)).

Psychosocial characteristics (having a steady partner, depressive symptoms, tobacco and alcohol consumption, adherence to ART, and self-reported symptoms), as well as biological characteristics (anaemia, the indicator of liver fibrosis, and the indicator of renal impairment) were evaluated at each visit and used as time-varying covariates in the statistical analyses. In the case of a missing value for any time-varying covariate, the last available value before the current visit was carried forward. All other variables (see Table 2) were used as fixed covariates, measured at M0, M1 or M4, as we wished to assess the effect of pre-ART or early clinical-immunovirological characteristics on mortality.

Statistical methods

The main characteristics at enrolment were compared between the 1,057 patients selected for this study and the 1,281 patients enrolled in the cohort, using Chi-2 tests and nonparametric Wilcoxon signed-ranks tests.

The follow-up period was defined for each patient as the period from M4 until his/her dropout from the cohort (i.e. the last follow-up visit with an available completed self-administered questionnaire) or death. The association between the composite indicator of social vulnerability and mortality was assessed after adjustment for all potential predictors and confounding factors, using a shared-frailty Cox proportional hazards (PH) model. This model is an extension of the standard Cox PH model, able to take into account informative study dropout (48). In the shared-frailty Cox model the patients were grouped into clusters according to their dropout time, each cluster having a specific baseline hazard ratio (individuals in the same cluster shared the same baseline hazard ratio, so that their times of death were correlated). Further details about the shared-frailty Cox model are provided in the Appendix. The number of clusters was assessed by plotting the cumulative hazard function for death according to three categories

defined by the patients' dropout time: before M20, between M20 and M60, and after M60 (see Figure 1). This allowed us to identify two main patterns, corresponding to two clusters defined by a dropout time before or after 60 months, respectively (individuals having their last available self-administered questionnaire before M60 were more likely to die than the others, due to unobserved heterogeneity). As is the case with most self-reported health-related data, the dropout time was very likely to be informative, as the sickest patients were more likely to have missing data.

Potential adjustment variables having a liberal significance level of $P < 0.20$ (Wald test) in the univariate analyses were considered eligible for inclusion in the multivariate analysis. A backward selection procedure was then used to select adjustment variables in the final multivariate model (variables were considered significantly associated with the outcome if $P \leq 0.05$). A likelihood ratio (LR) test (see Appendix) was used to test the shared-frailty Cox PH specification versus the standard Cox PH specification in the final multivariate model. Plausible interactions were assessed by creating interaction terms and adding them to the main effects model to test for their significance.

Stata/SE 12.1 for Windows (49) software was used for all analyses.

Results

The main characteristics of the 1,057 patients selected for this study were not significantly different from those of the 1,281 patients enrolled in the cohort in terms of gender, age, and clinical characteristics at baseline (results not shown).

The 1,057 patients selected for this analysis had a median (IQR) total follow-up period of 7.9 (3.0;11.2) years, representing 7,379 person-years (counting from 4 months of follow-up onwards). The dropout time (i.e. the maximum follow-up time corresponding to a completed self-administered questionnaire) was before M20, between M20-M60 and after M60 for, respectively, 20%, 22% and 58% of the selected patients.

A total of 147 deaths occurred in the cohort, among which 17 patients had not a completed self-administered questionnaire at M0 and 9 deaths occurred during the first 4 months of follow-up. The other 121 deaths, occurring between M4 and M144 among the 1,057 selected patients, were included in this study, corresponding to an overall mortality rate [95% confidence interval (CI)] of 1.64 [1.37;1.96] per 100 person-years from 4 months after ART initiation onwards.

The main causes of death were non-AIDS defining cancers ($n=26$), AIDS ($n=23$) and cardiovascular diseases ($n=12$). The causes of death are described in detail in Table 1. The selected patients were mostly males (78%) and their median age at enrolment was 36 years [interquartile range (IQR), 32;42]. Of the 1,057, 41% were infected through sex between men, and 17% through IDU. A quarter (25%) was born outside of Europe. At M4, 58%, 18%, 4% and 20% reported, respectively, low, moderate, elevated, and no alcohol consumption. Nineteen percent smoked more than 20 cigarettes/day and a third of patients reported depressive symptoms.

With respect to the four binary socio-economic indicators used in the MCA, the prevalence of 'No' answers was 65%, 41%, 20%, and 14% for, respectively, having a high school certificate, being employed, housing stability and housing comfort at M0 (see Table 2). The solution with two dimensions was retained in the MCA, explaining 58% of the total variance (35.6% and 22.5% for the first and second dimensions, respectively). Eigenvalues were 1.4 and 0.9 for the first and second dimensions, respectively. The first dimension distinguished 'Yes' and 'No' categories, with all 'No' categories located close to the negative side of the first axis and all

‘Yes’ categories located close to its positive side. Accordingly, the first factor of the MCA can be interpreted as a measure of good ‘general’ socio-economic status. We defined an indicator measuring ‘social vulnerability’ given by the reversed sign of the first factor, so that higher values of the indicator correspond to higher levels of social vulnerability. This composite indicator of social vulnerability varied between -2.60 and 1.33, with a median [IQR] of -0.35 [-0.47;0.51]. The employment item provided the highest contribution to this social vulnerability indicator (the corresponding discrimination measures for employment status, housing stability, education level and housing comfort were 0.48, 0.34, 0.34 and 0.27, respectively).

With regard to clinical characteristics, 44% of the selected patients were treatment naive, a quarter (25%) had been diagnosed more than 8 years before enrolment in the cohort (i.e. before the initiation of a PI-containing therapy), 20% had already experienced progression to AIDS before enrolment, 37.6% had a CD4 cell count below 200 cells/mm³, 30.1% had a plasma HIV RNA level greater than 100,000 copies/mL and approximately 22% were HCV-coinfected at M0. Table 2 shows factors potentially associated with mortality (univariate and multivariate analyses). Among the socio-behavioural factors, social vulnerability (as measured by the composite indicator), the presence of depressive symptoms and the number of self-reported symptoms causing discomfort were all associated with a higher risk of death.

With respect to clinical correlates eligible for the multivariate model, patients infected through sex between men were at lower risk of mortality. Conversely, patients with the following characteristics had a significantly higher risk of mortality: HCV coinfection, AIDS at M0 (i.e. progression to AIDS before ART initiation), longer delays between HIV diagnosis and ART initiation, plasma HIV RNA values over 100,000 copies/mL at enrolment, no increase over 200 CD4 cell count after initial 4 months of treatment, time-varying anaemia and indication of advanced liver fibrosis.

In our study, no significant association (no main effect and no confounding effect) was found in univariate analyses between mortality risk and the following known correlates and confounders: gender, time since ARV initiation at M0, renal impairment, having a steady partner, regular binge drinking, smoking > 20 cigarettes/day, and adherence to ART.

In the multivariate analysis (Table 2), higher levels of social vulnerability (HR [95% CI]=1.2 [1.0;1.5]) were independently associated with higher mortality risk, after adjustment for other significant known correlates as follows: age, AIDS stage at M0, plasma HIV RNA>100,000 copies/mL at enrolment (HR [95% CI]=1.7 [1.0;2.9]), poor early immune status (CD4 counts/mm³<200 at both M0 and M4) (HR [95% CI]=2.3 [1.3;4.1]), being antiretroviral naive and time since HIV diagnosis, anaemia (HR [95% CI]=2.4 [1.5;3.7]), advanced liver fibrosis during follow-up (HR [95% CI]=2.5 [1.5;4.3]) and low alcohol consumption (≤ 1 AU/day, versus no consumption) (HR [95% CI]=0.6 [0.4;1.0]). With regard to the interaction effects, a significant relationship between being antiretroviral naive and increased mortality risk was found only among patients who had been diagnosed more than 8 years before enrolment in the cohort (HR [95% CI]=2.8 [1.4;5.4]). Accordingly, time since diagnosis was an effect modifier for being antiretroviral naive at enrolment. Furthermore, the clinical CDC stage at enrolment was an effect modifier for age as the association between age and increased mortality risk was significant among the patients in stage A or B (HR [95% CI]=1.3 [1.1;1.7]), but not significant among the patients in stage C at enrolment.

The results of the LR test ($P<10^{-3}$) seemed to favour the shared-frailty Cox PH model over the standard Cox PH model, as they provided strong evidence for the existence of significant latent patient frailty.

Discussion

This is the first study to explore the effect of social vulnerability on mortality in a French national cohort of HIV-infected patients receiving ART. It shows that mortality risk increases by 20% per each unit increase of the social vulnerability index, even when taking other known clinical and behavioural predictors of mortality into account.

This study also shows that non-AIDS related cancers are the first cause of mortality today, while AIDS-related causes of death (including AIDS-defining cancers) constitute the second cause. The burden of co-infection is apparent, as in this cohort – which is representative of individuals exposed not only to the first generation of combined ART (i.e., PI-containing regimens) but also to suboptimal HBV and HCV care - the third most common cause of death was related to HCV or HBV associated complications. As a number of unknown causes of death were present in the study, we preferred to focus on overall mortality without any distinction of the cause.

To date, only one study, conducted in the US in the ART era, has shown that HIV-infected participants meeting the US government's definition of poverty were more likely to die than others. Specifically, it found they were 1.5 times more likely to die (30). As our model is adjusted for longer periods since HIV diagnosis, for poor early immune status during the first four months of ART and for HIV plasma viral load before starting ART, we can presume that the most socially vulnerable patients were also those more likely to have encountered difficulties with adherence and to have experienced complications of immunosuppression or undiagnosed/untreated co-morbidities over the long term course of ART treatment.

The association between social vulnerability and mortality is even more striking in a country like France where access to care is free for anyone (all residents in France are covered by health insurance by law; most qualify for state health insurance, which generally reimburses 70% of patients' costs). This association reflects the fact that socially vulnerable individuals have to first cope with financial worries before thinking about their health status. It is worth noting that such populations tend to use emergency services more than the rest of the HIV-infected population (50), this greater utilization being an indicator of missed opportunities for early detection of severe comorbidities (given that non-AIDS related cancers are the first cause of death) or risk factors for acute fatal events (cardiovascular events were the third most common cause of death in this cohort).

Moreover, social vulnerability is often associated with psychiatric disorders, such as depressive symptoms, which were a major predictor of clinical progression in a previous analysis on the same cohort (51). It may also be correlated with addictive behaviours which may increase the risk of acute non-HIV related mortality (i.e. overdoses, suicides, road accidents, etc.) (52, 53).

Our results are consistent with other studies which showed that low socio-economic status and education are associated with increased mortality in HIV-infected individuals before and during the era of potent antiretroviral therapy (16-18, 26-29) and remain valid after adjustment for known significant correlates of mortality, as anaemia (56-58) or the indicator of liver fibrosis. This confirms recent trends indicating a decrease of HIV-related mortality, but also an increase in competing mortality causes related to liver-associated damage or comorbidities (3, 15). One Danish study (59) recently tried to disentangle the effects of (i) pre-treatment factors, in particular HIV-related risk factors (AIDS-defining diseases and insufficient response to ART), (ii) comorbidities including hepatitis C, and (iii) behaviours (drug and excessive alcohol use), on overall mortality. It concluded that in HIV patients with no risk factors, the probability of survival was equivalent to that of the general population while the main burden of mortality was

attributable to behaviours. However, that study did not take into account the changing pattern of predictors over time and factors like social vulnerability.

AIDS clinical stage at ART initiation remained a major predictor of mortality. The effect of clinical stage was so strong that it cancelled out the effect of age, the latter remaining significant only in patients who had not experienced progression to AIDS at enrolment. This result may be due to the specificity of the enrolled patients in the cohort.

Finally, we found an association between very low alcohol consumption and reduced mortality risk, which is in line with previous results for the same cohort (62), which showed that individuals with low alcohol consumption presented higher CD4 cell-counts. We do not know whether this association is more a proxy of general healthy habits or just "a French paradox", and further investigation in other cohorts is needed to verify this result. It is worth noting that some of the most important mortality risk factors, like elevated tobacco or alcohol use, were not associated with mortality risk in this study. This was perhaps due to the fact that lifetime cumulative exposure to alcohol or tobacco could not be computed, as this was not the original objective of the study. We did not find any effect of behavioural changes in elevated alcohol or tobacco use during follow-up (data not shown), perhaps because cumulative exposures may counterbalance certain possible positive effects of abstinence.

Our choice to use a shared-frailty Cox PH model specification, able to take into account informative study dropout, was justified by the results of the LR test for the existence of latent frailty depending on the cluster (dropout time before or after M60). Accordingly, the usual interpretation of effects based on the standard Cox PH model specification would not have been appropriate.

Some limitations of the study need to be mentioned. First, our results concern a HIV-infected population which is not representative of the population initiating ART today. This is because a non-negligible proportion of our study population (non-treatment naive patients) had been exposed to sub-optimal treatments before ART initiation, which is no longer the case for those starting treatment today. This may have resulted in increased mortality rates, although being antiretroviral naive was not significantly associated with mortality.

Furthermore, our study shows that even in the French national context of free access to care, social vulnerability still plays a role in the inequality of ART care. Although it is difficult to generalize our results to other countries, the impact of social vulnerability may be even stronger in countries where access to HIV care is not free for everyone.

While the use of a fixed baseline measure of social vulnerability may seem to be another limitation of the study, in reality it is not for two reasons. First, we recomputed the composite indicator at different specific follow-up times but it did not greatly evolve over time (data not shown). Second, we aimed to emphasize the importance for HIV clinicians to timely identify patients who, by combining several different sources of vulnerability due to their social conditions, require more comprehensive care, more frequent follow-up visits and ad hoc social interventions in order to obtain better response to ART.

To conclude, this study underlines the fact that social vulnerability is a major risk factor of mortality. Free access to HIV care is not enough to make HIV a chronic condition and ensure active ageing of people living with the disease. A real need exists for innovative social interventions targeting individuals cumulating several sources of social vulnerability, in order to protect their right to health care and to ensure that social inequalities do not continue to be a source of higher mortality among them.

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Authors' contribution:

Camelia Protopopescu analyzed the data and wrote the manuscript; François Raffi was responsible for cohort initiation, contributed to patients' recruitment and investigation and revised the manuscript; Bruno Spire contributed to data analyses and revised the manuscript; Lucile Hardel contributed to patients' evaluation; Christian Michelet contributed to patients' recruitment and investigation; Christine Cheneau contributed to patients' recruitment and investigation; Vincent Le Moing contributed to patients' recruitment and investigation and revised the manuscript; Catherine Leport was responsible for cohort initiation, contributed to patients' recruitment and investigation and revised the manuscript; Maria Patrizia Carrieri planned the data analyses and wrote the manuscript. All authors approved the final version of the manuscript.

Previous presentations: Preliminary results have been presented in a poster at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (30th June-3th July 2013, Kuala Lumpur, Malaysia), the 14th European AIDS Conference (16th-19th October 2013, Brussels, Belgium), and the 18th International Workshop on HIV Observational Databases (27th–29th March 2014, Sitges, Spain).

Disclosure statement: All authors have no conflicts of interest to declare.

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Table 1. Causes of deaths, the ANRS CO8 APROCO-COPILOTE cohort (M4-M144)

Causes of deaths	n (%)
Non AIDS-related cancer	26 (21.5)
AIDS-related	23 (19)
Unknown	12 (9.9)
Cardiovascular diseases	12 (9.9)
Accident/aggression	11 (9.1)
HCV or HBV	10 (8.3)
Other infectious and parasitic diseases	7 (5.8)
Overdose	5 (4.1)
Suicide	5 (4.1)
Digestive diseases	4 (3.3)
Unexplained sudden death	3 (2.5)
Benign tumours	1 (0.8)
Respiratory diseases	1 (0.8)
Endocrine, nutritional and metabolic diseases	1 (0.8)
Total	121 (100)

Table 2. Characteristics of the study population and factors associated with deaths (shared-frailty Cox proportional hazards model, univariate and multivariate analyses, the ANRS CO8 APROCO-COPILOTE cohort, M4-M144)

	N (%) or median [IQR] at time origin^{§§}	Univariate analyses		Multivariate analysis	
		HR [95% CI]	P- value	AHR [95% CI]	P- value
Clinical CDC stage at M0 & Age					
Clinical CDC stage C at M0	215 (20.3)	9.0 [1.4;57.7]	0.021	6.2 [0.8;48.7]	0.082
Age for patients in stage C at M0	38 [34;45]	0.7 [0.4;1.0]	0.050	0.9 [0.6;1.4]	0.614
Age for patients in stage A-B at M0	36 [32;42]	1.0 [0.8;1.2]	0.973	1.3 [1.1;1.7]	0.010
Antiretroviral naive & Time since HIV diagnosis at M0					
Antiretroviral naive & time since diagnosis < 8 years at M0	377 (35.7)	0.8 [0.5;1.2]	0.350	1.0 [0.6;1.7]	0.963
Antiretroviral naive & time since diagnosis ≥ 8 years at M0	83 (7.8)	2.9 [1.7;5.0]	0.000	2.8 [1.4;5.4]	0.003
Not antiretroviral naive at M0	595 (56.3)	1		1	
Coinfection with HCV at M0					
No	779 (73.7)	1			
Yes	231 (21.8)	1.8 [1.2;2.6]	0.003		
CD4+ cell count/mm³ at M0 & M4					
≥ 200 at M0	660 (62.4)	1		1	
< 200 at M0 and ≥ 200 at M4 (at M1 if missing)	235 (22.2)	1.2 [0.7;1.9]	0.569	0.6 [0.3;1.2]	0.191
< 200 at M0 and < 200 at M4 (at M1 if missing)	114 (10.8)	3.1 [1.9;4.9]	0.000	2.3 [1.3;4.1]	0.006
Plasma HIV RNA at M0 (copies/mL)					
≤ 100,000	736 (69.6)	1		1	
> 100,000	318 (30.1)	2.2 [1.5;3.2]	0.000	1.7 [1.0;2.9]	0.032
Haemoglobin[§] (g/dL)					
≥ 13(12) for men(women)	881 (83.3)	1		1	
< 13(12) for men(women) (anemia)	176 (16.6)	2.7 [1.8;4.0]	0.000	2.4 [1.5;3.7]	0.000

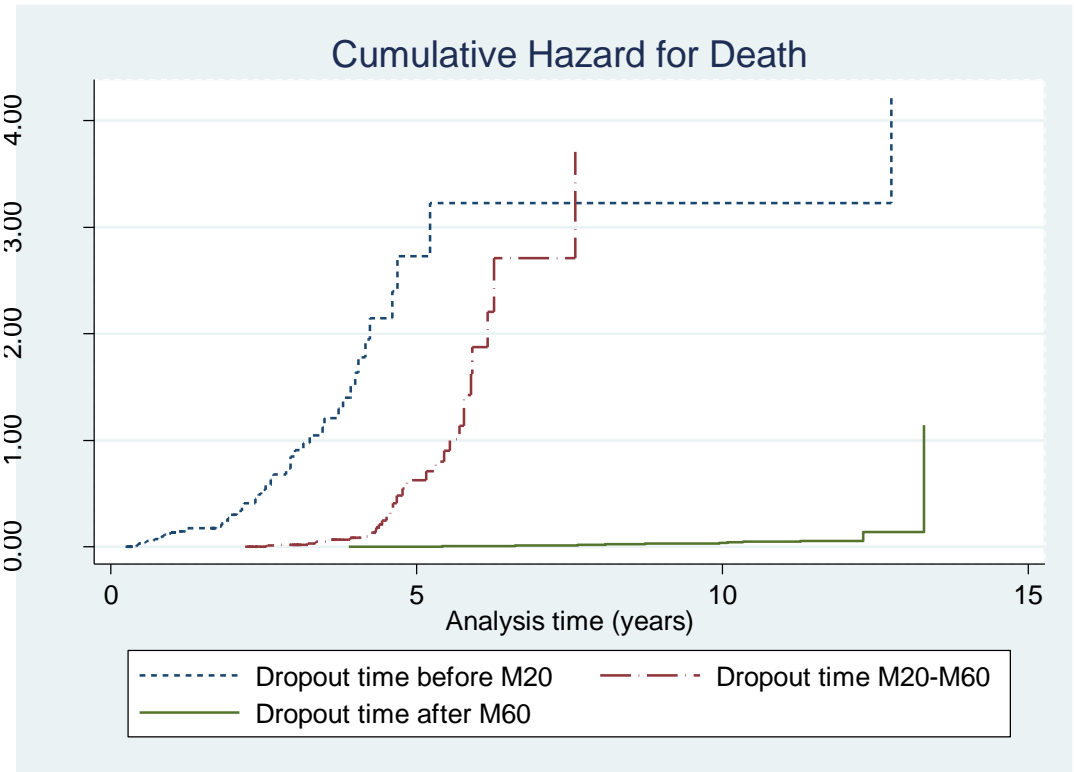
Indicator of liver fibrosis FIB-4[§]					
≤ 3.25	998 (94.4)	1		1	
> 3.25 (advanced fibrosis)	59 (5.6)	3.1 [2.0;4.9]	0.000	2.5 [1.5;4.3]	0.000
HIV transmission category					
IDU	181 (17.1)	1.2 [0.8;1.8]	0.437		
Sex between men	438 (41.4)	0.5 [0.3;0.8]	0.003		
Other	438 (41.4)	1			
High school certificate at M0					
No	686 (64.9)	1			
Yes	352 (33.1)	0.7 [0.5;1.1]	0.162		
Being employed at M0					
No	434 (41.1)	1			
Yes	575 (54.4)	0.7 [0.4;0.9]	0.043		
Stable housing at M0					
No	217 (20.5)	1			
Yes	840 (79.5)	0.7 [0.4;1.0]	0.066		
Comfortable housing at M0					
No	147 (13.9)	1			
Yes	888 (84.0)	0.6 [0.4;1.0]	0.056		
Social vulnerability indicator at M0 (from MCA)	-0.35 [-0.47;0.51]	1.3 [1.1;1.6]	0.003	1.2 [1.0;1.5]	0.033
Depressive symptoms[§]					
No (CES-D ≤ 17(23) for men(women))	695 (65.7)	1			
Yes (CES-D > 17(23) for men(women))	356 (33.7)	1.9 [1.3;2.7]	0.001		
Alcohol consumption[§] (AU/day)					
No consumption	212 (20.1)	1		1	
Low (≤ 1)	614 (58.1)	0.4 [0.2;0.6]	0.000	0.6 [0.4;1.0]	0.044
Moderate (> 1 and ≤ 4(3) for men(women))	188 (17.8)	0.6 [0.4;1.0]	0.070	0.8 [0.4;1.6]	0.628
Elevated (> 4(3) for men(women))	43 (4.1)	0.5 [0.5;1.2]	0.118	0.7 [0.2;1.8]	0.459

IQR = interquartile range; (A)HR = (adjusted) hazard ratio; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression scale; HCV = hepatitis C virus; AU = alcohol unit; IDU = injection drug use; CDC = Centers for Disease Control and Prevention

§ Time-varying variable

§§ The frequencies are reported at M0 for fixed variables, and at the first available visit between M4-M144 for time-varying variables

Figure 1. Cumulative hazard function for death according to the dropout time (before M20, between M20 and M60, after M60), the ANRS CO8 APROCO-COPILOTE cohort (M4-M144)



Appendix

The shared-frailty Cox proportional hazards (PH) model

The conditional hazard function of the model, given the unobserved frailty variable w_i for the i th cluster and the covariate vector x_{ij} is defined by:

$$h(y|w_i, x_{ij}) = h_0(y)w_i \exp(x'_{ij}\beta)$$

where β is the vector of unknown model coefficients, $h_0(\cdot)$ is the baseline hazard ratio common to all subjects, x_{ij} is the covariate vector for the j th subject in the i th cluster, and the frailty variables w_i are assumed to be independently Gamma distributed with a mean of 1 and unknown variance θ_i . The interpretation of regression coefficients β remains the same as in the standard Cox PH model, but is conditionally made on the frailty variables w_i which explicitly account for the extra variance associated with unmeasured risk factors.

A likelihood ratio (LR) test for the variance of the frailty variable (LR test for $\theta_i = 0$) was used to compare the shared-frailty Cox PH specification versus the standard Cox PH specification.